AIMS CENTER
UNIVERSITY of WASHINGTON
Psychiatry & Behavioral Sciences
Advancing Integrated Care for Over 20 Years

# Major Depressive Disorder and Treatment with Antidepressants in Primary Care Settings

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*Slide credits to Mark Duncan, MD, and Jessica Whitfield, MD, MPH*

# Planner & Speaker Disclosures

- The following speaker and planners have no relevant conflicts of interest to disclose:
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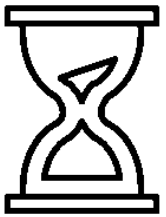
# Discussion



What questions do you have about treating depression in your patient population?

# Learning Objectives

- Review the diagnosis of major depressive episodes.
- Identify initial treatments for major depressive episodes.
- Discuss essential prescribing practices for antidepressants for people with MDD.

# DSM-5 Major Depressive Episode

- 5+ symptoms present during 2-week period (at least 1 is depressed mood or loss of interest/pleasure)
  - Depressed mood
    - NOTE: In children and adolescents, can be irritable mood
  - Markedly diminished interest/pleasure in activities
  - Significant weight loss (not dieting) or weight gain (e.g., >5% change of body weight in a month) or appetite change
    - NOTE: In children, consider failure to make expected weight gain
  - Insomnia or hypersomnia
  - Psychomotor agitation or retardation (observable by others, not merely subjective feelings of restlessness or being slowed down)
  - Fatigue or loss of energy
  - Feelings of worthlessness or excessive/inappropriate guilt (not merely self-reproach or guilt about being sick)
  - Diminished ability to think or concentrate, or indecisiveness
  - Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without specific plan, suicide attempt, or specific plan for suicide
- Symptoms cause clinically significant distress or impaired functioning.
- Episode not attributable to substance use or another medical condition.

# Other Causes of Depressive Symptoms

- Persistent depressive disorder
- Premenstrual dysphoric disorder
- Substance-induced depressive disorder
- PTSD
- Seasonal affective disorder
- Depressive disorder due to a medical condition (ex: sleep apnea, thyroid, anemia, hormonal changes, dementia)
- Adjustment disorder
- Bipolar disorder
  - The majority of presentations of bipolar disorder to primary care are depressive phase!
  - Need to rule out bipolar disorder as most antidepressants do not work or make it worse, trigger hypo/mania

# Prevalence of Major Depressive Episode in US

- 2021
  - Major depressive episode
    - 21.0 million adults (8.3%)
  - Major depressive episode with impairment
    - 14.5 million adults (5.7%)

*NIMH Major Depression Statistics*

# Depression in Primary Care

- Epidemiology:
  - —Primary care: 5–25% of patients with depressive symptoms
  - —60% of people with depression don't get treatment
    - Those who do: up to 50% get treatment in primary care!

*Akincigil et al., 2015, Smithson et al., 2017; Lakiss et al., 2015*

# Screening

- USPSTF, AAFP: Universal, if adequate treatment and follow-up in place
- Screening tools to consider:
  - Depression: PHQ-2 vs PHQ-9
  - Substances: AUDIT-C and DAST-10
  - Perinatal: Edinburgh Postnatal Depression Scale or PHQ-9 in pregnant/postpartum people
  - Bipolar disorder: CIDI to rule out bipolar disorder (MDQ less specific)
  - Lab work: TSH, CBC, B12, Vit D, folate, BMP
  - Sleep apnea: STOP-BANG, sleep study

*Management of MDD – VA/DoD Clinical Practice Guidelines (2022)*

# PHQ-9

| Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✔" to indicate your answer)* | Not at all | Several days | More than half the days | Nearly every day |
|---|---|---|---|---|
| **1.** Little interest or pleasure in doing things | 0 | 1 | 2 | 3 |
| **2.** Feeling down, depressed, or hopeless | 0 | 1 | 2 | 3 |
| **3.** Trouble falling or staying asleep, or sleeping too much | 0 | 1 | 2 | 3 |
| **4.** Feeling tired or having little energy | 0 | 1 | 2 | 3 |
| **5.** Poor appetite or overeating | 0 | 1 | 2 | 3 |
| **6.** Feeling bad about yourself — or that you are a failure or have let yourself or your family down | 0 | 1 | 2 | 3 |
| **7.** Trouble concentrating on things, such as reading the newspaper or watching television | 0 | 1 | 2 | 3 |
| **8.** Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual | 0 | 1 | 2 | 3 |
| **9.** Thoughts that you would be better off dead or of hurting yourself in some way | 0 | 1 | 2 | 3 |

FOR OFFICE CODING 0 + _____ + _____ + _____

=Total Score: _____

**If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?**

| Not difficult at all | Somewhat difficult | Very difficult | Extremely difficult |
|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ |

# Acute Phase (6–12 weeks): Initiating Treatment

- Contact should occur: 1 week after initiation of treatment, then every 2–4weeks until remission or response
- Use shared decision making to decide on initial treatment
  - **Mild**: Monotherapy antidepressants or psychotherapy(ex. BA)
  - **Moderate**: Pharmacotherapy or psychotherapy (ex. CBT or IPT) or combination
  - **Severe**: Preferred combination pharmacotherapy and psychotherapy (ex. CBT or IPT); Consider interventional approaches (ex. ECT)

*Weihs & Wert, 2011*

# Considerations for Treatment of Uncomplicated Depression

- For initial treatment, select pharmacotherapy, psychotherapy, or both based on shared decision-making
- If previous treatment was successful, consider restarting this approach
- Based on patient preferences, consider self-help with exercise (ex. yoga, tai chi, aerobics, etc.), light therapy, patient education, and bibliotherapy
- Include patient characteristics (ex. co-occurring disorders, pregnant patients, geriatric patients) in shared decision making
- Consider Collaborative Care in primary care for appropriate patients

*Management of MDD—VA/DoD Clinical Practice Guideline (2022)*

# Antidepressants and MDD

- Do antidepressants work for MDD?
  - Yes
  - And…SNRIs and mirtazapine may work a little better
  - And…there will be a range of responses (average 2–4 point improvement on HAM-D)
- Do antidepressants only work for severe depression?
  - No—they work to the same degree in mild to severe depression

*Levkovitz et al., 2011; Cipriani et al., 2011*

# Selective Serotonin Reuptake Inhibitors

| Drug | Usual total daily starting dose (mg) | Usual total daily dose (mg) | Extreme daily dose range (mg) |
|---|---|---|---|
| Citalopram | 20 | 20–40 | 10–40 |
| Escitalopram | 10 | 10–20 | 5–30 |
| Fluoxetine | 20 | 20–60 | 10–80 |
| Fluvoxamine | 50 | 100–200 | 25–300 |
| Fluvoxamine CR | 100 | 100–200 | 100–300 |
| Paroxetine | 20 | 20–40 | 10–50 |
| Paroxetine CR | 25 | 25–50 | 12.5–62.5 |
| Sertraline | 50 | 50–200 | 25–300 |

# Serotonin–Norepinephrine Reuptake Inhibitors

| Drug | Usual total daily starting dose (mg) | Usual total daily dose (mg) | Extreme daily dose range (mg) |
|---|---|---|---|
| Desvenlafaxine | 25–20 | 50–100 | 50–400 |
| Duloxetine | 30–60 | 60 | 30–120 |
| Levomilnacipran | 20 | 40–80 | 20–120 |
| Milnacipran | 12.5 | 100–200 | 50–300 |
| Venlafaxine | 37.5–75 | 75–375 | 75–375 |
| Venlafaxine XR | 37.5–75 | 75–375 | 75–375 |

# Atypical Agents

| Drug | Usual total daily starting dose (mg) | Usual total daily dose (mg) | Extreme daily dose range (mg) |
|---|---|---|---|
| Agomelatine (not available in US) | 25 | 25–50 | 25–50 |
| Bupropion | 200 | 300 (max. single dose 150) | 100–450 |
| Bupropion SR 12 hour | 150 | 300 (max. single dose 200) | 150–400 |
| Bupropion XL 24 hour | 150 | 300 | 150–450 (US)<br>150–300 (Europe) |
| Bupropion hydrobromide 24 hour | 174 | 348 | 174–522 |
| Mirtazapine | 15 | 15–45 | 7.5–60 |

# Serotonin Modulators

| Drug | Usual total daily starting dose (mg) | Usual total daily dose (mg) | Extreme daily dose range (mg) |
|---|---|---|---|
| Nefazodone | 200 | 300–600 | 50–600 |
| Trazodone | 100 | 200–400 | 100–600 |
| Vilazodone | 10 | 40 | 10–40 |
| Vortioxetine | 10 | 20 | 5–20 |

# Shared Decision Making

- Ask patients about their beliefs about medications and expectations for treatment.
- Common Considerations:
  - Anticipated side effects
  - Pharmacologic properties (half-life, med interactions)
  - Past response to med
  - Family history of response
  - Depressive symptoms
  - Comorbid illnesses


[Depression Medication Choice Decision Aid (mayoclinic.org)]

# Considerations for People of Reproductive Age

- Pregnancy:
  - Consider psychotherapy or phototherapy for mild to moderate depression.
  - Antidepressant medication indicated for severely depressed patients and patients who don't respond to non-pharmacological interventions.
  - Risks of untreated depression: Increased risk of preterm labor and low birth weight, reduced fetal growth, and delayed infant language development.
  - Paroxetine should be avoided during pregnancy. Transient neonatal effects can occur among newborns exposed to SSRIs in utero.
  - For severe cases of depression, consider electroconvulsive therapy (ECT).
- Breast-feeding:
  - Infant exposure to first-line antidepressants is slight or negligible with breastfeeding.
  - Sertraline has short half-life so is preferred antidepressant for breastfeeding patients.
  - Not generally recommended to switch antidepressants among patients stabilized on another agent.

# Additional Considerations

| Consideration | Best Choice |
|---|---|
| No anxiety | Bupropion |
| With anxiety | Sertraline, venlafaxine |
| With tobacco dependence and/or ADHD | Bupropion |
| Insomnia and underweight | Mirtazapine |
| Insomnia and desire to avoid weight gain | Sertraline + short duration of sleep aid<br>Escitalopram + short duration of sleep aid |
| Chronic pain | Duloxetine; amitriptyline or augmentation with gabapentin |

# Treatment-Resistant Depression

- 2–3 antidepressants failed
  - —Augment antidepressant with aripiprazole
    - Most double-blind evidence of all augmenters
  - —Augment antidepressant with bupropion/lithium
  - —Switch to SNRI
  - —MAOI (usually tranylcypromine)
  - —ECT
  - —Esketamine nasal or ketamine infusion

# Timing

- How fast can antidepressants work?
  - 1–2 weeks
  - Change dose every 2–4 weeks
- How long should I wait before changing medications?
  - 6–12 weeks
  - Potentially sooner if no response

*Taylor et al., 2006; Rush, 2007*

# Adverse Effects from Antidepressants

| Adverse effect | Associated medications | Time to onset |
|---|---|---|
| Gastrointestinal bleeding | SSRIs, esp. when used with nonsteroidal anti-inflammatory or antiplatelet drugs; risk mitigated by acid-suppressing medications | Anytime during treatment |
| Hepatoxicity | Nefazodone, bupropion, duloxetine, trazodone | Anytime during treatment |
| Hyponatremia (sodium < 130 mEq per L [130 mmol per L]) | SSRIs, SNRIs, mirtazapine, TCAs | Within first month |
| Osteoporosis and fractures | SSRIs, SNRIs | Over 10 years |

*Pharmacologic Treatment of Depression | AAFP*

# Adverse Effects from Antidepressants, cont.

| Adverse effect | Associated medications | Time to onset |
|---|---|---|
| QT prolongation (dose dependent) | Citalopram, escitalopram, amitriptyline<br><br>FDA warns against exceeding recommended citalopram dose: ≤ 60 years old, 40 mg daily; > 60 years, 20 mg daily | At initiation; typically dependent on coexisting risk factors |
| Sexual adverse effects | Trend toward increased risk with escitalopram and paroxetine; decreased risk with bupropion | Within first week |
| Suicidality (age related with increased risk <18 years) | Duloxetine, fluoxetine, paroxetine, sertraline, venlafaxine | Not defined |
| Weight gain (> 5%) | SSRIs, SNRIs, TCAs; decreased risk with bupropion | Over 10 years (highest risk in first two years) |

*Pharmacologic Treatment of Depression | AAFP*

# Serotonin Syndrome

**Rare but dangerous potential complication associated with serotonergic antidepressants when patients are taking other medications that increase serotonin or in overdose.**

- Exposure to increased serotonergic activity of meds includes:
  - Overdose with a serotonergic agent (except direct serotonin receptor agonist)
  - Drug–drug interaction of 2 serotonergic agents (except when both are direct serotonin receptor agonists)
  - Initiation/dose increase of serotonergic agent or agent that decreases metabolism of serotonergic agent
- Examples of agents with serotonin activity:
  - Increase serotonin release (e.g., cocaine, mirtazapine)
  - Impair serotonin reuptake (e.g., SNRIs, SSRIs, meperidine)
  - Inhibit MAO (e.g., Linezolid, selegiline)
  - Increase receptor sensitivity (e.g., lithium)
  - Increase serotonin formation (e.g., tryptophan)

# Continuation Phase

- Are there things to do to make antidepressants work better?
  - —See patients frequently at the beginning of treatment
  - —Continue to titrate as needed
  - —Provide education about the illness and treatments
  - —Build therapeutic alliance
    - Be curious
    - Validate
    - Listen

*Thase, 2011*

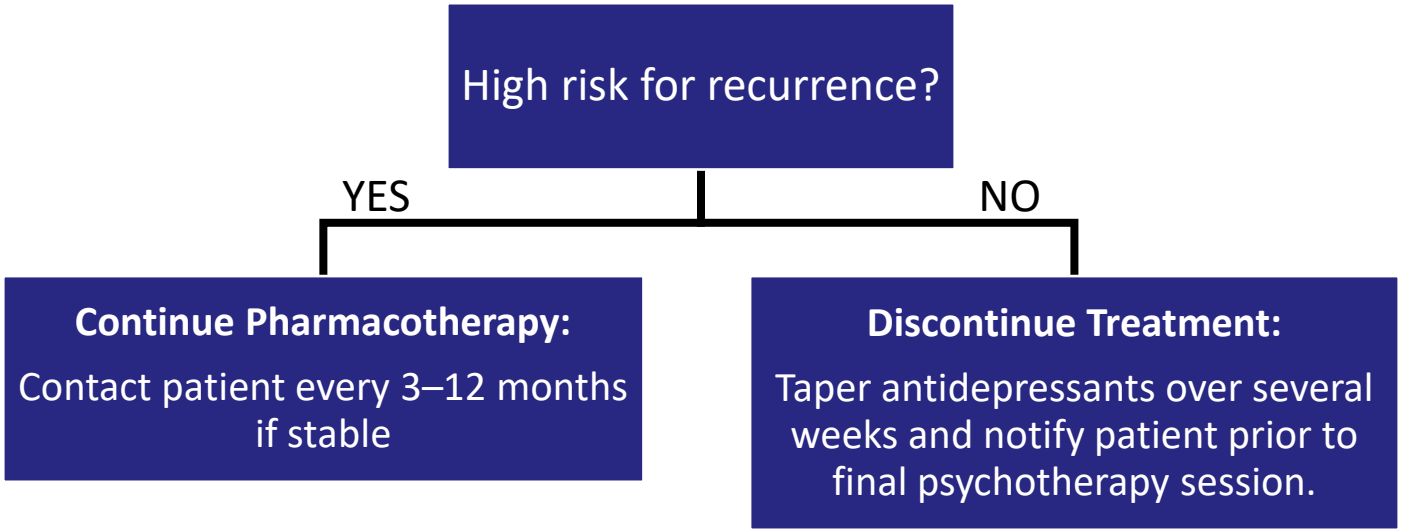
# Long Term and Discontinuation Phase

- One year to lifetime
- Randomized control trial in UK, 150 clinics
  - Inclusion:
    - 478 patients
    - 2+ depressive episodes OR antidepressants for 2+ years
  - Over 1-year period, discontinuation group had higher relapse rate (56%) vs maintenance group (39%)

*Lewis et al., 2021*

# How Long to Continue Antidepressants

- Risk Factors for Recurrence:
  - 3+ major depressive episodes OR 2 prior episodes and any of the following factors:
    - Chronic major depressive disorder
    - Present or residual symptoms
    - Ongoing psychological stressors
    - Early age of onset
    - Family history of mood disorders




*Lewis et al, 2021*

# Antidepressant Withdrawal

| | |
|---|---|
| F | • Flu-like symptoms |
| I | • Insomnia |
| N | • Nausea |
| I | • Imbalance |
| S | • Sensory disturbance |
| H | • Hyperarousal (anxiety/agitation) |

- AKA discontinuation syndrome
- Higher risk: shorter half-life, abrupt or more rapid taper
- Evidence for CBT, maintenance antidepressants

*Maund et al., 2019; Fornaro et al., 2023; Gabriel et al., 2017*

# Tapering Strategies for Antidepressant Medications

| Strategy | Description | Example | Comments |
|---|---|---|---|
| 10% reduction per week | Reduce dose every 4 weeks to match 10% reduction in serotonin transporter occupancy | Citalopram (each dose for 4 weeks): 40 mg → 20 mg → 19 mg → 9.1 mg → 5.4 mg → 3.4 mg → 2.3 mg → 1.5 mg → 0.8 mg → 0.37 mg | Formulated using pharmacokinetic data but difficult to precisely implement |
| 3- to 4-month taper | Reduce dose by 25% every 4 weeks or by 12.5% every 2 weeks | Citalopram (each dose for 4 weeks): 40 mg → 30 mg → 20 mg → 15 mg → 10 mg → 7.5 mg → 5 mg → 2.5 mg | Easier to accomplish in real-world practice, but linear dose decrease may still result in antidepressant discontinuation syndrome |

*Pharmacologic Treatment of Depression | AAFP*

# Tapering Strategies, pt 2

| Strategy | Description | Example | Comments |
|---|---|---|---|
| Cross taper | Slowly decrease dose of current med while increasing dose of new med | Citalopram (current med, 40-mg starting dose) and sertraline (new medication), each dosage combo for 2-4 weeks:<br>30 mg cit., 12.5 mg ser.<br>20 mg cit., 18.75 mg ser.<br>15 mg cit., 25 mg ser.<br>10 mg cit., 37.5 mg ser.<br>7.5 mg cit., 50 mg ser.<br>5 mg cit., 75 mg ser.<br>2.5 mg cit., 100 mg ser. | Exposure to multiple serotonergic agents has inherent risks<br>Potential for cytochrome P450-mediated drug reactions depending on drug choice<br>Increased pill burden and financial strain for patients |
| Direct switch | Start new med immediately after discontinuing current one | Discontinue citalopram, 20 mg<br>Initiate sertraline, 50 mg | May be difficult to determine if patient-reported adverse effects are due to new agent or antidepressant discontinuation syndrome |

*Pharmacologic Treatment of Depression | AAFP*

# Tapering Strategies, pt 3

| Strategy | Description | Example | Comments |
|---|---|---|---|
| Moderate switch | Current med tapered down, followed by washout period of 2–3 days<br><br>New med initiated at conservative dose, then increased | Citalopram (current med), each dosage for 4 weeks: 20 mg → 15 mg → 10 mg → 7.5 mg → 5 mg → 2.5 mg<br><br>Discontinue for 2–3-day washout period<br><br>Start sertraline (each dosage for 4 weeks): 25 mg → 37.5 mg → 50 mg | Potential for antidepressant discontinuation syndrome due to drug-free period<br><br>More time consuming but considered safer |
| Conservative switch | Current med tapered down, followed by washout period of 4 or 5 half-lives<br><br>New med initiated at conservative dose, then increased | Same as moderate switch but with longer washout period (7 days for most drugs, except those with long half-lives, e.g., fluoxetine) | Potential for antidepressant discontinuation syndrome due to drug-free period<br><br>Patients must wait longer for treatment benefit from new medication |

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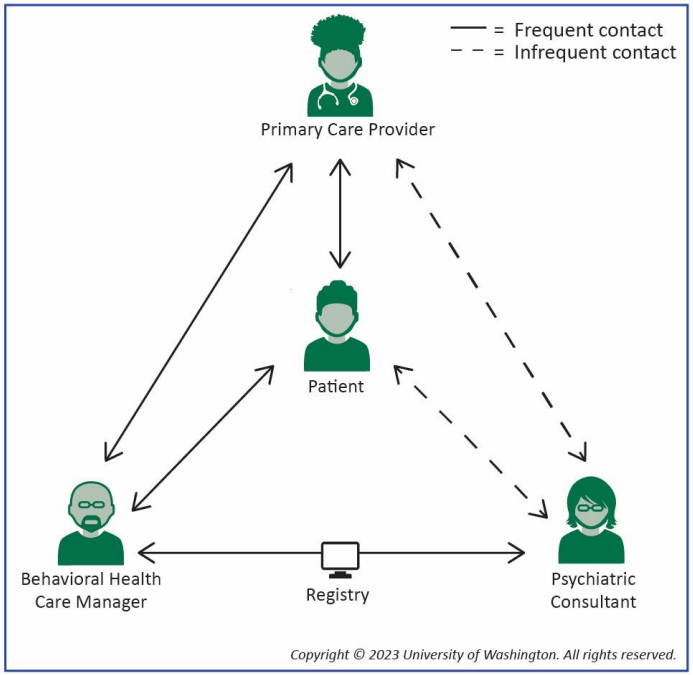
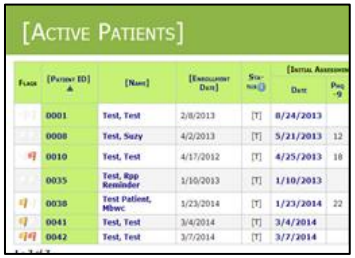
# Collaborative Care (CoCM)

Primary care patient-centered team-based care




Systematic Caseload Review with Psychiatric Consultant (focus on patients not improved)




Registry to track population

Cognitive Behavioral Therapy (CBT)
Interpersonal Therapy (IPT)
Behavioral Activation (BA)
Medications

Active treatment with evidence-based approaches


Validated outcome measures tracked over time

# Working as a Team: Evidence-Based Medication Treatment

- PCP Approaches
  - Medications are safe and effective but patients will likely need adjustment in antidepressant treatment to achieve remission
  - First-line medications are SSRIs, SNRIs, bupropion, and mirtazapine, which all have comparable efficacy but different side effect profiles
- BHCM Approaches
  - Support assessment of past medication trials
  - Assess for potential barriers to engaging in medication management (e.g., cost or cultural barriers)
  - Support patients through making medication changes and troubleshoot adherence challenges

# Working as a Team: Evidence-Based Behavioral Treatment

- PCP Approaches
  - Validate behavioral interventions are treatment; Consider giving the patient a prescription for these treatments
  - Assess engagement with and reinforce behavioral treatment during medical visits
- BHCM Approaches
  - There are many evidence-based behavioral interventions for depression that can be delivered briefly in primary care medicine
  - First-line treatments include BA, CBT, IPT, and PST

# Case Introduction

- A 53-year-old man presents to his PCP with primary complaint of "not sleeping enough, having headaches, and feeling run down"
  - For the last 4 months, he has been waking up too early in the morning and cannot get back to sleep
  - During the day, he is exhausted and has trouble focusing when he's at work
  - His chronic back pain has increased, so he has been staying at home and has stopped exercising
  - He has tried everything he can think of to "break out of this rut" but feels like it is pointless and is ready to give up
- PHQ-9 score 18
  - Patient said that he never thought of himself as depressed before
- PCP did safety assessment to follow up on the patient's thoughts of giving up and determined passive SI
- PCP introduced CoCM

# Case: Warm Connection with BHCM

- Behavioral Health Care Manager visit—conducted comprehensive assessment of patient
  - He has been more irritable with his wife and children for the past 6 months and stopped going out with friends
  - In the last 2 weeks, he has been late to work 4 times because he can't get himself started in the morning
  - Additional history revealed he had a similar episode in the past when he was about 20 years old when he was having trouble with his coursework at the college; talked with a college counselor for several months
  - Has started smoking cigarettes again after having quit 4 years ago
- With permission, BHCM contacted the patient's wife in his presence
  - Discussed passive suicidality, which wife had not known about
  - Wife was grateful to be included in the assessment, no additional concerns

# Case: Making a Diagnosis

- PCP:
  - Review of systems was notable for headaches and exacerbation of chronic back pain.
  - Minimal alcohol use on the CAGE and does not use opioids.
  - Patient has hypertension, but blood pressure is in the normal range on hydrochorothiazide
  - Physical exam (including neurological exam) unremarkable
  - No lab tests indicated
- BHCM:
  - Screened for substance use—negative and confirmed that the patient did not have a prior history of drug or alcohol problems.
  - GAD-7 score = 6
  - Additional screening for PTSD (PCL-C) and bipolar disorder (CIDI-3)—both negative
- → Provisional diagnosis of major depressive disorder

# Case: Initiating Treatment

- Systematic Caseload Review
  - BHCM and Psychiatric Consultant discussed patient presentation
  - Psychiatric Consultant suggested bupropion as initial antidepressant, given efficacy in supporting smoking cessation
    - Provided titration schedule to escalate dose to therapeutic range and monitor response with PHQ-9 over 4–6 weeks
  - BHCM to offer behavioral activation (BA) to patient and support antidepressant management
- BHCM Visit
  - BHCM explained rationale behind BA and what to expect from treatment
  - BHCM consulted with PCP about activities patient could safely engage in, given chronic back pain
- PCP Visit
  - BHCM updated PCP about treatment plan and antidepressant recommendations
  - PCP prescribed bupropion SR 150mg daily
  - PCP reinforced BHCM's role in coordinating care and value of BA for depression to patient

# Case: Monitoring Treatment with Measurement-Based Care

- At week 4:
  - Patient's sleep and energy improving, but PHQ-9 score still at 14.
  - BHCM notified the PCP—increased bupropion SR dose to 150 mg twice daily (morning and afternoon), as suggested by Psychiatric Consultant
- At week 8:
  - Patient reported concentration improving at work and back pain had improved; PHQ-9 score was down to 8
  - Continued on bupropion 150 mg twice daily and ongoing follow-up with the BHCM for behavioral activation. BHCM taught ways to manage negative thoughts
- At week 12:
  - Patient's PHQ-9 dropped to 4, and he reported pain was more manageable
  - Patient reported adding to his walking routine, feeling better connected socially, decrease in irritability, and better relationships with family
  - BHCM recommended follow-up appointments be reduced to every other month

# Case: Concluding Episode of Care and Relapse Prevention

- After another 4 months:
  - Patient's PHQ-9 score dropped to 1, and he reported continued success in social engagement, even when his back bothered him
  - Patient and BHCM began to discuss relapse prevention plan, including:
    - Continuing medication for another year,
    - Plan to continue his pleasant activities (walking, swimming, socializing with family and friends, volunteering at the local church on Sundays)
    - Continuing to track symptoms on own and a plan to monitor "hot" symptoms (indicators he may need to check in with PCP)
    - If PHQ-9 >5 for 2 weeks, experienced unremitting pain for 1 week, or began dropping activities, patient would contact PCP for follow-up

# Questions?